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FOCUS ISSUE: TRANSCATHETER CARDIOVASCULAR THERAPEUTICS

A Multicenter Randomized Trial Comparing Amphilimus- With Paclitaxel-Eluting Stents in De Novo Native Coronary Artery Lesions

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Objectives This study sought to demonstrate the noninferiority of polymer-free amphilimus-eluting stents (Cre8, CID, Saluggia, Italy) versus permanent-polymer paclitaxel-eluting stents (Taxus Liberté, Boston Scientific, Natick, Massachusetts) in de novo percutaneous coronary intervention.

Background Although the efficacy of the drug-eluting stent has been well established, the risk-benefit balance is still suboptimal, and the safety of polymers remains uncertain.

Methods Patients undergoing percutaneous coronary intervention for de novo lesions were randomly assigned 1:1 to Cre8 or Taxus Liberté stents. Primary endpoint was 6-month angiographic in-stent late lumen loss (LLL) within a noninferiority scope. Six-month intravascular ultrasound was performed in 20% of the patients. All patients will be clinically followed up to 5 years.

Results Out of 323 patients enrolled, 162 received Cre8 and 161 Taxus Liberté stents. In-stent LLL was significantly lower in Cre8 group (0.14 ± 0.36 mm vs. 0.34 ± 0.40 mm, p noninferiority <0.0001, p superiority <0.0001). Clinical endpoints (cardiac death, myocardial infarction, target lesion revascularization, and stent thrombosis) up to 12 months did not differ significantly between the groups.

Conclusions The Cre8 stent in de novo lesions showed significantly lower in-stent LLL at 6 months than the Taxus Liberté stent did, with a trend toward better 12-month clinical safety and efficacy results. (International Randomized Comparison Between DES Limus Carbostent and Taxus Drug-Eluting Stents in the Treatment of De Novo Coronary Lesions [NEXT]; NCT01373502) (J Am Coll Cardiol 2012;59:1371–6) © 2012 by the American College of Cardiology Foundation

Drug-eluting stents (DES) represent a breakthrough technology that has profoundly affected the treatment of coronary artery disease (1,2). Most DES are composed of metallic stent platform, antiproliferative drug agent, and its carrier, most frequently a polymer, which modulates drug diffusion into the vessel wall and release kinetics. Although mid-term DES efficacy has been well established, there is an increased incidence of late stent thrombosis (3,4), particularly after discontinuation of thienopyridine therapy.

A strategy to limit the potential negative influence of this serious event was the introduction of biodegradable polymers (5,6). Nevertheless, several in vivo investigations still reported an extensive inflammatory response (7–9).

Therefore, the best strategy to overcome these drawbacks is a polymer-free (PF) metallic DES (10,11) or a bioresorbable DES (12).

The Cre8 stent (CID, Saluggia, Italy) PF DES was studied, in a prospective single-blinded randomized mul-

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Abbreviations and Acronyms

CK = creatine kinase
DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
LLL = late lumen loss
MI = myocardial infarction
PF = polymer-free
PP = permanent polymer
QCA = quantitative coronary angiography
TLR = target lesion revascularization

ticenter trial, for noninferiority in terms of 6-month angiographic in-stent LLL compared to permanent-polymer (PP) Taxus Liberté (Boston Scientific, Natick, Massachusetts).

Methods

Study design and patient selection. Patients from 11 centers were randomly assigned in a single-blinded fashion to receive either Cre8 or Taxus Liberté (Taxus). Patients were eligible if they had stable or unstable angina or silent ischemia with single de novo lesions ≤20 mm length, at a maximum 2 different coronary arteries with a diameter ranging from 3.0 to 3.75 mm. Major exclusion criteria were percutaneous coronary intervention within 30 days, acute myocardial infarction within 72 h, renal failure, left ventricular ejection fraction ≤30%, or other significant comorbidities.

Angiographic exclusion criteria were left main disease, bifurcation and ostial lesions, chronic total occlusions, presence of severe calcification, or excessive tortuosity. The study was approved by each participating institution's ethics committees, conducted according to good clinical practice and Helsinki's Declaration. All patients provided written informed consent.

Study device. The Cre8 stent is a polymer-free stent with a thin (80-μm) cobalt-chromium alloy L605, integrally coated by an ultra-thin (0.3-μm) passive carbon coating (i-Carbofilm, CID, Saluggia, Italy). The amphilimus formulation, constituted by sirolimus (0.9 $\mu g/mm^2$) formulated with an excipient composed of long-chain fatty acids mixture, to modulate the drug release, is loaded into abluminal reservoirs to obtain a targeted elution toward the vessel wall.

Randomization and masking. A computer-generated blocked randomization list was used to allocate patients on a 1:1 basis to one of the study arms and to the intravascular ultrasound (IVUS) substudy. Allocation was insured by sequentially numbered and sealed envelopes. Patients, members of the clinical event committee, and angiographic and IVUS core laboratory personnel were masked to treatment allocation.

Study procedures. Randomized patients received a Cre8 or a Taxus stent after the lesion was crossed by the guidewire. Sixty patients, 30 in each arm, were also selected for IVUS substudy, at 3 pre-selected sites.

Pre-dilation was mandatory. Available stent sizes were 3.0 and 3.5 mm, whereas stent lengths ranged from 12 to 25 mm.

Periprocedural anticoagulation with heparin or bivalirudin and administration of glycoprotein IIb/IIIa inhibitors was according to local practice. Post-procedure dual-antiplatelet therapy was mandated for at least 6 months, with indefinite continuation of aspirin. Electrocardiograms were recorded at baseline and within 24 h after the procedure. Creatine kinase (CK) and CK-myocardial band fraction were measured at baseline and within 12 to 24 h after stenting. All patients underwent angiographic follow-up at 6 months and clinical follow-up at 30 days, 6 months, and annually thereafter for 5 years.

Data management, endpoints, and definitions. Collected data were monitored, with 100% verification against source data, and entered into an electronic database (Oracle Clinical, Redwood Shores, California).

Clinical events (death, myocardial infarction, stent thrombosis, revascularization procedures, and cerebrovascular events) were adjudicated by an independent clinical event committee.

Primary endpoint was 6-month angiographic in-stent LLL measured by quantitative coronary angiography (QCA). Secondary clinical endpoints included death, myocardial infarction (MI) (according to the World Health Organization definition based on CK and CK-myocardial band rise) (13). Target lesion revascularization (TLR) (defined as repeat PCI or coronary artery bypass graft of the target lesion), target vessel revascularization (defined as repeat PCI or coronary artery bypass graft of the target vessel) and composite endpoints of major adverse cardiac events (death, MI, and TLR), target vessel failure (cardiac death, target vessel-related MI, clinically driven TLR, or target vessel revascularization), TLF (cardiac death, target

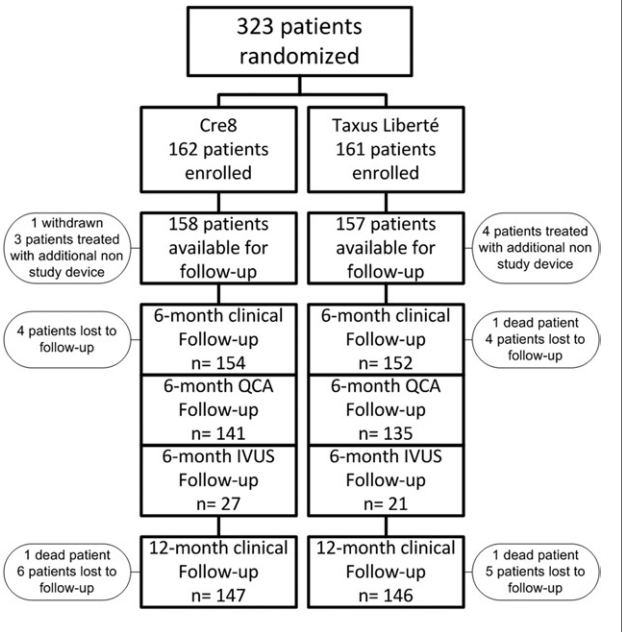

Figure 1 Trial Profile Showing the Number of Randomized Patients

IVUS = intravascular ultrasound; QCA = quantitative coronary angiography.

vessel–related MI, clinically driven TLR), and stent thrombosis were adjudicated according to the Academic Research Consortium classification (14). Secondary endpoints also included device success (attainment of <30% in-stent residual stenosis of the target lesion, by QCA, using the assigned device) and procedure success (attainment of a final lesion success and no in-hospital major adverse cardiac events up to 7 days after the index procedure).

Quantitative coronary angiography. All angiograms acquired using standardized instructions were analyzed by an independent core laboratory (Bioclinica, Leiden, the Netherlands). The QCA was performed using standard image quantification software (Medis, Leiden, the Netherlands). LLL was defined as the difference between minimal lumen diameter immediately after the procedure and 6-month minimal lumen diameter (MLD), diameter stenosis was calculated as: [1 − (MLD/RVD)] × 100 (RVD is the reference vessel diameter). Binary restenosis was defined as a reduction of 50% or more of the luminal diameter in the target lesion. Measurements were obtained within the stent (in-stent) and within the segment (in-segment, including the stented segment and 5 mm proximal and distal to the stent).

Intravascular ultrasound. Serial IVUS imaging was performed after stent implantation and at 6-month follow-up. Quantitative IVUS measurements were performed by independent core laboratory (Bioclinica) using dedicated software (Medis).

Table 1 Clinical and Lesion Characteristics

	Cre8* (n = 162)	Taxus Liberté* (n = 161)
Demographics		
Age, yrs	64.90 ± 10.20	64.39 ± 10.45
Male	124/162 (76.5)	109/161 (67.7)
Risk factors		
Current smoking	39/162 (24.1)	40/161 (24.8)
Dyslipidemia	102/162 (63)	98/161 (60.9)
Diabetes		
ID diabetes	10/162 (6.2)	11/161 (6.8)
Non-ID diabetes	38/162 (23.5)	28/161 (17.4)
Hypertension	104/162 (64.2)	104/161 (64.6)
History		
Prior myocardial infarction	14/162 (8.6)	15/161 (9.3)
Prior PCI	26/162 (16.0)	23/161 (14.3)
Targeted coronary artery		
LAD	86/188 (45.7)	90/189 (47.6)
LCX	48/188 (25.5)	39/189 (20.6)
RCA	54/188 (28.7)	60/189 (31.7)
Lesion type, ACC/AHA		
A	37/188 (19.7)	36/189 (19.0)
B1	102/188 (54.3)	101/189 (53.4)
B2	35/188 (18.6)	45/189 (23.8)
C	14/188 (7.4)	7/189 (3.7)
Moderate or severe calcification	44/188 (23.4)	35/185 (18.5)
Lesion length, mm	15.41 ± 6.99	15.15 ± 7.08

Values are mean ± SD or n/N (%). *For all comparisons, p = NS.
ACC/AHA = American College of Cardiology/American Heart Association; ID = insulin-dependent; LAD = left anterior descending artery; LCX = left circumflex artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

Table 2 Quantitative Coronary Angiography

	Cre8	Taxus Liberté	p Value
Before procedure	(n= 181 lesions)	(n = 184 lesions)	
RVD, mm	2.76 ± 0.42	2.79 ± 0.43	0.5051
MLD, mm	0.98 ± 0.36	1.00 ± 0.38	0.5475
DS, %	64.26 ± 11.35	64.11 ± 11.56	0.8996
After procedure			
RVD, mm	2.92 ± 0.40	2.91 ± 0.44	0.8481
In-stent MLD, mm	2.62 ± 0.37	2.64 ± 0.39	0.7488
In-segment MLD,* mm	2.35 ± 0.43	2.35 ± 0.47	0.9943
In-stent DS, %	9.99 ± 7.33	9.03 ± 8.04	0.2373
In-segment DS,* %	17.56 ± 8.64	18.10 ± 8.47	0.5549
6-month follow-up	(n = 160 lesions)	(n = 156 lesions)	
RVD, mm	2.86 ± 0.36	2.84 ± 0.42	0.5727
In-stent MLD, mm	2.50 ± 0.47	2.31 ± 0.48	0.0006
In-segment MLD,* mm	2.25 ± 0.47	2.14 ± 0.48	0.0353
In-stent DS, %	12.58 ± 12.23	18.66 ± 11.45	<0.0001
In-segment DS,* %	20.53 ± 11.75	24.72 ± 11.95	0.0022
Late lumen loss			
In-stent, mm	0.14 ± 0.36	0.34 ± 0.40	<0.0001†
In-segment,* mm	0.11 ± 0.36	0.23 ± 0.36	0.0041
Binary restenosis			
In-stent	5 (3.1)	3 (2.0)	0.7239
In-segment*	5 (3.2)	6 (4.0)	0.7664

Values are mean ± SD or n (%). *In-segment includes the 5-mm segments proximal and distal to the stent edges; late lumen loss indicates difference between MLD at 6 months and MLD after the procedure; and DS >50% at follow-up. †The p value indicates both noninferiority and superiority.
DS = diameter stenosis; MLD = minimal lumen diameter; RVD = reference vessel diameter.

Statistical analysis. The study sample size was determined based on the primary endpoint of 6-month in-stent LLL, assuming no difference in mean, a noninferiority delta of 0.16 mm, and a standard deviation of 0.50 mm.

Given these assumptions, 250 subjects would have provided an 80% power to demonstrate the noninferiority between the 2 groups. To account for dropout and to ensure enough angiographic data, approximately 300 patients were required. For continuous variables, differences between groups were evaluated by Student *t* test, whereas for discrete variables chi-square or Fisher exact tests were used. Normality of angiographic endpoints' distribution was verified and Wilcoxon-Mann-Whitney test was adopted instead of Student *t* test when appropriate.

The p value for noninferiority was 1-tailed, and all other p values were 2-tailed. Statistical significance was set at the 0.05 level for superiority and 0.025 for noninferiority.

Kaplan-Meier cumulative incidence estimates were used to analyze outcome events, which were compared between groups using the log-rank test.

Statistical analysis, performed by CID company and independently reviewed by the study coordinating investigator, was conducted according to implanted study devices. In total, 8 patients were excluded: 7 received additional nonstudy stents in the target lesion (3 patients

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in Cre8 and 4 in Taxus), and 1 in Cre8 group withdrew from the study.

Results

From October 2009 to September 2010, 323 patients were enrolled: 162 were assigned to Cre8 and 161 to Taxus groups (Fig. 1). In addition, 48 patients (27 treated with Cre8 and 21 treated with Taxus) were included in the IVUS substudy. Baseline clinical presentation and lesion characteristics were similar between groups (Table 1).

Quantitative coronary angiography. Pre- and post-procedure QCA measurements were performed on 315 patients with 365 lesions (181 Cre8, 184 Taxus).

Six-month angiographic parameters (Table 2) were analyzable for 276 subjects with 316 lesions (160 Cre8, 156 Taxus). All angiographic endpoints except minimal lumen diameter were nonnormally distributed, irrespective of implanted device.

In-stent LLL primary endpoint was lower for Cre8 than for Taxus (0.14 ± 0.36 mm vs. 0.34 ± 0.40 mm), reaching statistical significance both for noninferiority ($p < 0.0001$) and for superiority ($p < 0.0001$). In-stent 6-month diameter stenosis was also significantly lower for Cre8 (12.6 ± 12.2% vs. 18.7 ± 11.4%, $p < 0.0001$) (Fig. 2A). Cumulative in-stent LLL frequency showed a median value of 0.07 mm for Cre8 versus 0.27 mm for Taxus (Fig. 2B). Significant differences in favor of the Cre8 group were also shown for other QCA parameters, whereas no difference was found for in-stent binary restenosis (3.1% vs. 2.0%) (Table 2).

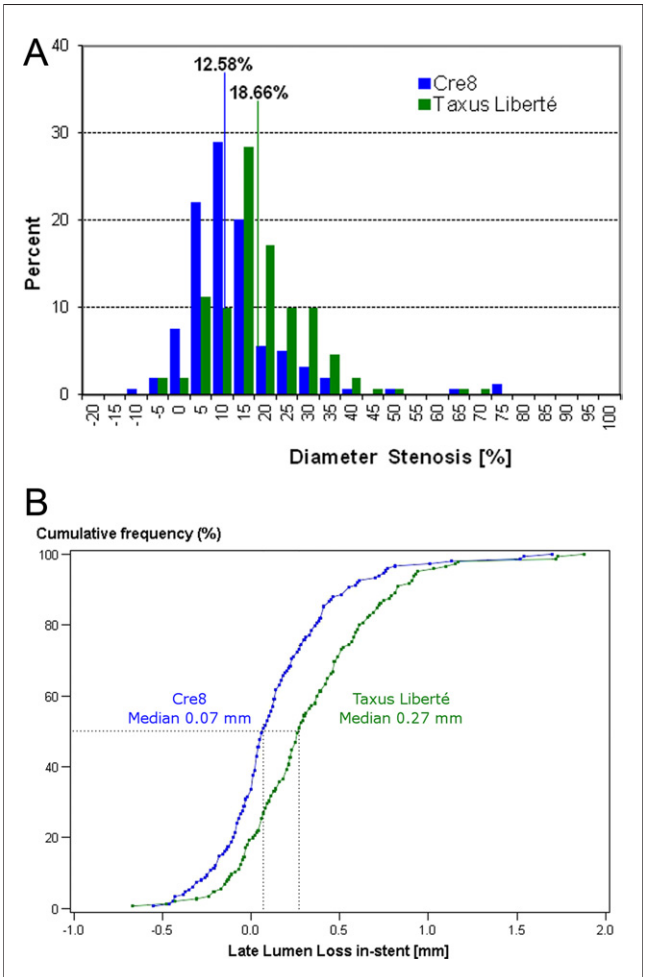

Figure 2 6-Month Angiographic Follow-Up

(A) Distribution of 6-month diameter stenosis (with lines showing mean values). **(B)** Cumulative frequency of late lumen loss.

Table 3 Clinical Outcomes at 12 Months

	Cre8 (n = 148)	Taxus Liberté (n = 148)	p Value
Death, all	2/148 (1.4)	3/148 (2.0)	1.0000
Cardiac	2/148 (1.4)	1/148 (0.7)	1.0000
Noncardiac	0/148 (0)	2/148 (1.4)	0.4983
MI, all	1/148 (0.7)	2/148 (1.4)	1.0000
Q-wave	1/148 (0.7)	2/148 (1.4)	1.0000
Non–Q-wave	0/148 (0)	0/148 (0)	—
Repeat revascularization, all	13/148 (8.8)	12/148 (8.1)	0.8344
TLR	7/148 (4.7)	9/148 (6.1)	0.6072
Clinically driven	4/148 (2.7)	1/148 (0.7)	0.3707
Nonclinically driven	3/148 (2.0)	8/148 (5.4)	0.2177
TVR	6/148 (4.1)	3/148 (2.0)	0.5010
Composite endpoints, hierarchical			
MACE*	9/148 (6.1)	10/148 (6.8)	0.8125
TLF*	6/148 (4.1)	3/148 (2.0)	0.5010
TVF*	15/148 (10.1)	13/148 (8.8)	0.6912
Stent thrombosis			
Definite	1/158 (0.6)	1/157 (0.6)	1.0000
Acute	0/158 (0)	0/157 (0)	—
Subacute	0/158 (0)	1/157 (0.6)	0.4984
Late	1/158 (0.6)	0/157 (0)	1.0000
Probable	0/158 (0)	0/157 (0)	—
Acute	0/158 (0)	0/157 (0)	—
Subacute	0/158 (0)	0/157 (0)	—
Late	0/158 (0)	0/157 (0)	—
Possible	2/158 (1.3)	0/157 (0)	0.4984
Acute	0/158 (0)	0/157 (0)	—
Subacute	0/158 (0)	0/157 (0)	—
Late	2/158 (1.3)	0/157 (0)	0.4984

Values are n/N (%). *MACE is the composite of cardiac death, MI, and TLR. TLF is the composite of cardiac death, target vessel MI, and clinically indicated TLR. TVF is the composite of all death, MI, and all repeat revascularization.

MACE = major adverse cardiac events; MI = myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization.

Post hoc subgroup analysis focusing on 82 diabetic patients (44 lesions Cre8 and 39 Taxus Liberté) confirmed the significantly lower LLL associated with Cre8 (0.12 ± 0.28 mm vs. 0.43 ± 0.41 mm, $p < 0.0001$).

Intravascular ultrasound. Six-month IVUS analysis was available in 48 patients (27 Cre8, 21 Taxus). The Cre8 stent proved superior for the pre-specified IVUS endpoints of neointimal hyperplasia volume (11.8 ± 8.2 mm^3 vs. 18.7 ± 10.1 mm^3, $p = 0.009$) and volume obstruction (6.7 ± 2.4% vs. 11.3 ± 5.6%, $p = 0.001$).

Clinical outcomes. Cumulative 12-month clinical outcomes showed no significant differences between study arms in any of the assessed clinical outcomes (Table 3), although

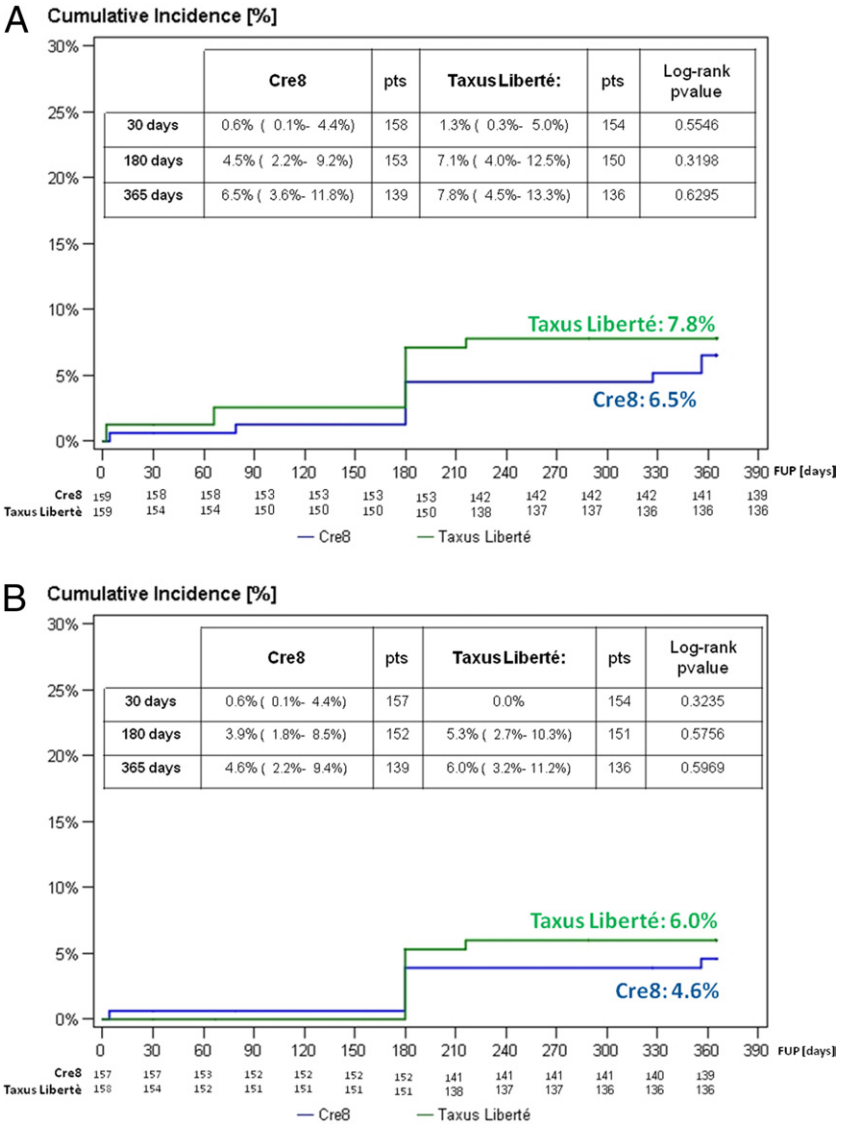

Figure 3 **Major Adverse Cardiac Events at 12-Month Follow-Up**

(A) Any major adverse cardiac event. **(B)** Target lesion revascularization.

there was a trend toward more frequent events in the Taxus arm (Figs. 3A and 3B). The same trend was maintained in the diabetic subset (major adverse cardiac events: 4.5% vs. 11.1%, respectively, for Cre8 and Taxus, p = NS).

TLR were performed in 7 patients (4.7%) treated with Cre8 stents and in 9 patients (6.1%) treated with Taxus stents. Moreover, 3 patients experienced MI: 2 in the Taxus group (1.4%), 1 due to a spontaneous dissection in a nontarget vessel and 1 related to definite stent thrombosis; 1 in Cre8 arm (0.7%), related to a definite stent thrombosis. The patient implanted with Taxus was later found to be a nonresponder to clopidogrel, whereas the subject who received the Cre8 stent interrupted the aspirin therapy and was later found to be a nonresponder to thienopyridine due to genetic mutation. Three cardiac deaths occurred: 2 patients (1.4%), implanted with Cre8, died suddenly 3 and 11 months after the index procedures. One patient (0.7%), who received a Taxus stent, had a cardiac arrest due to a spontaneous dissection in a nontarget vessel 2 months after the procedure. One (0.7%) vascular death, related to fatal cerebral bleeding, and 1 (0.7%) noncardiovascular death due to sepsis occurred in the Taxus arm.

Discussion

This is the first study to assess the role of the Cre8 stent. This technology, based on PF abluminal reservoir elution, may remove a major cause of late stent thrombosis, which still remains a DES limitation (1–4), namely the vessel wall

exposure to potentially proinflammatory polymers and to drug residues on the stent luminal side, which may impair the vessel healing. Pathological studies have suggested inflammation caused by PP as a potential cause (7–9).

Pre-clinical studies, performed on Cre8 using a PP Cypher stent (Cordis, Miami Lakes, Florida) as a control have shown a reduced neointimal thickness and inflammatory score, as well as a drug washout, into the systemic circulation, that is significantly lower than the one for Cypher. Moreover, the amphilimus formulation was completely eluted from the reservoirs within 3 months, leaving an iCarbofilm-coated stent behind (15).

These distinctive Cre8 features may take a role in reducing the need for prolonged dual-antiplatelet therapy.

In the clinical setting, the present noninferiority study achieved its primary endpoint, demonstrating that PF Cre8 was noninferior, and even superior, to PP Taxus in terms of 6-month LLL. The IVUS analysis further supported the superior antirestenotic efficacy of Cre8, demonstrating significantly lower neointimal hyperplasia and volume obstruction.

The relative efficacy of different DES in diabetic patients remains controversial. Paclitaxel has been postulated to be a particularly effective drug in diabetic patients (16), when compared to everolimus (Xience, Abbott Vascular, Abbott Park, Illinois) in SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) trials (17), but sirolimus, eluted from a PP Cypher stent, has always been detected as superior in inhibiting the restenotic process (18,19). The present post-hoc analysis on diabetics evidenced a statistically significant lower LLL and a trend toward better clinical outcomes for the Cre8 stent, compared with the Taxus stent, suggesting superior efficacy of the PF amphiphilic sirolimus formulation.

Study limitations. Taxus was chosen as a comparator as it was the most widely used DES when the study was designed. The 6-month angiographic control may not have captured the point of maximum LLL for either stent. However, 12-month outcomes significantly correlate with later clinical outcomes. Larger studies and longer follow-up are needed to thoroughly assess clinical endpoints.

Conclusions

The Cre8 stent in de novo lesions showed significantly lower in-stent LLL at 6 months than the Taxus Liberté stent did, with a trend toward better 12-month clinical safety and efficacy results.

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Key Words: coronary artery disease ■ drug-eluting stent(s) ■ percutaneous coronary intervention ■ randomized controlled trial.